In the claims:

Please amend claims 1 and 6 as follows:

1. **(Amended)** A method for monitoring the effects of a pathology differentiating agent on a tissue sample, comprising:

applying a pathology differentiating agent on a tissue sample, wherein said pathology differentiating agent interacts with said tissue sample and alters its optical characteristics; and

monitoring the rate of change of light reflection from said tissue sample over time, thereby monitoring the effects of a pathology differentiating agent on a tissue sample.

6. **(Amended)** A method for the *in vivo* diagnosis of a tissue abnormality in a subject, comprising

contacting a tissue in a subject with a pathology differentiating agent, wherein said pathology differentiating agent interacts with said tissue sample and alters its optical characteristics;

exposing said tissue in said subject to optical radiation; and

monitoring the intensity of light emitted from said tissue over time, thereby diagnosing a tissue abnormality in a subject.

REMARKS

Claims 1-16 were pending in the application. Claims 1 and 6 have been amended. Accordingly, after the amendments presented herein have been entered, claims 1-16 will remain pending. For the Examiner's convenience these claims are set forth herein in Appendix A.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached page is captioned "Version With Markings to Show Changes Made".

Support for the amendments to claims 1 and 6 may be found throughout the specification, including the claims as originally filed. Specifically, support may be found at, for example, page 2, lines 7-10; page 4, lines 14-18; and page 16, lines 5-8 of the specification.

No new matter has been added. Any amendments to and/or cancellation of the claims

should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

The claims presented herein essentially correspond to the claims of U.S. Publication Number 20020007122A1 and U.S. Publication Number 20020127735A1. Independent claim 1 essentially corresponds to independent claims 1, 14, 16 and 25 of U.S. Publication Number 20020127735A1 and independent claim 6 essentially corresponds to independent claims 1, 2, 15, 18 and 27 of U.S. Publication Number 20020007122A1. Copies of U.S. Publication Number 20020007122A1 and U.S. Publication Number 20020127735A1 are submitted as part of the supplemental IDS which is submitted herewith.

U.S. Publication Number 20020007122A1 and U.S. Publication Number 20020127735A1

Applicant respectfully submits that U.S. Publication Number 20020007122A1 (the '122 application) and U.S. Publication Number 20020127735A1 (the '735 application) are not available as 35 U.S.C. §102(e) prior art against Applicant's invention for the following reasons. Applicant submits herewith a declaration under 37 CFR §1.131 which indicates that Applicant had completed the invention as described and claimed in the instant patent application in this country, a NAFTA country, or a WTO country, prior to ***December 15, 1999***. The '122 application and the '735 application both have an effective 35 U.S.C. §102(e) date of ***December 15, 1999***. Accordingly, Applicant respectfully submits that the invention disclosed in the present patent application was reduced to practice by the inventor prior to the effective date of the '122 application and the '735 application. As such, the '122 application and the '735 application are not available as prior art against the present invention under 35 U.S.C. §102(e).

The Balas C. et al. (December 1999) Journal of Photochemistry and Photobiology 53:153-157 Article

Exhibit A in the declaration under 37 CFR §1.131 which is submitted herewith is the article Balas C. *et al.* (December 1999) Journal of Photochemistry and Photobiology 53:153-157.

Applicant submits herewith a declaration under 37 CFR §1.132 which indicates that George C. Themelis, Emmanuel P. Prokopakis, Irene Orfanudaki, Eugenios Koumantakis and Emmanuel S. Helidonis, who are co-authors with the inventor in the Balas *et al.* (December 1999) paper, are *not* co-inventors of the subject matter described and claimed in the above-identified application. As indicated in the declaration, George C. Themelis was a graduate student in the lab of Dr. Balas who performed technical aspects described in the above-referenced paper under the direction and supervision of Dr. Balas. Emmanuel P. Prokopakis and Irene Orfanudaki were medical residents who performed technical aspects described in the above-referenced paper at the request and under the direction and supervision of Dr. Balas. Eugenios Koumantakis and Emmanuel S. Helidonis are directors at the clinics were the clinical work described in the above-referenced paper was performed and did not otherwise contribute to the work described in this publication.

Accordingly, the Balas C *et al.* (December 1999) article represents Applicant's own work, published within the year before the effective filing of the present application, and cannot be used against Applicant under 35 U.S.C.§ 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1958).

Objections to the Disclosure

The Examiner has objected to the disclosure "for containing minor errors in syntax and spelling" and has requested that the specification be reviewed to correct errors where they appear.

Applicant respectfully submits that the specification has been amended to correct several typographical errors, including the errors noted by the Examiner. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdrawn the foregoing objection to the specification.

Rejection of Claims 1, 2, 6, 7, 9, 10, 12, and 16 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 1, 2, 6, 7, 9, 10, 12, and 16 under 35 U.S.C. §102(b) as being anticipated by Klaveness *et al.* The Examiner relies on Klaveness *et al.* for disclosing "a method for monitoring the effects of a pathology differentiating agent on a tissue sample comprising applying a pathology differentiating agent on a tissue sample (see col. 29, lines 5-6) and monitoring the rate of change of light reflection from said tissue sample over time (see col. 29, lines 5-7 and col. 29, lines 10-11), thereby monitoring the effects of a pathology differentiating agent on a tissue sample."

Applicant respectfully traverses the forgoing rejection for the following reasons. As amended, claim 1 and claims depending therefrom, are directed to a method for monitoring the effects of a pathology differentiating agent on a tissue sample by applying a pathology differentiating agent on a tissue sample, ***wherein the pathology differentiating agent interacts with the tissue sample and alters its optical characteristics***; and monitoring the rate of change of light reflection from the tissue sample over time, thereby monitoring the effects of a pathology differentiating agent on a tissue sample. As amended, claim 6 and claims depending therefrom, are directed to a method for the *in vivo* diagnosis of a tissue abnormality in a subject, by contacting a tissue in a subject with a pathology differentiating agent, ***wherein the pathology differentiating agent interacts with the tissue sample and alters its optical characteristics***; exposing the tissue in the subject to optical radiation; and monitoring the intensity of light emitted from the tissue over time, thereby diagnosing a tissue abnormality in a subject.

For a prior art reference to anticipate in terms of 35 U.S.C. § 102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicant respectfully submits that Klaveness *et al.* do not teach or suggest the methods

of claims 1 and 6 and claims depending therefrom. Klaveness *et al.* disclose the introduction into an animal of ***particulate materials as scattering contrast agents***. These particulate materials may be directly imaged (where the particulate material comprises a chromophore or a fluorophore; see column 10, lines 45-62); may be used in contrast enhancement (where the particulate material can attenuate light differently than the surrounding tissue leading to contrast enhancement; see column 11, lines 4-7); or may serve as reflection centers (where the particulate material selectively directs the incident light to a detector; see column 11, lines 8-14). The particulate materials disclosed by Klaveness *et al.* ***do not interact with the tissue that is being imaged to cause an alteration in the optical characteristics of the tissue***. In contrast, Applicant's invention is based, at least in part, on the ability of the pathology differentiating agent to interact with the tissue being tested, thereby altering its optical characteristics. As taught in Applicant's specification, these pathology differentiating agents have the property of interacting with the altered metabolic and structural characteristics of a pathologic tissue, thereby altering the optical characteristics of the tissue (see, for example, page 4, lines 14-18 of the specification).

In summary, Applicant respectfully submits that the Klaveness particulate agents are scatterers/fluorophores/absorbers themselves. In contrast, the pathology differentiating agents used in the methods of the present invention are not scatterers/fluorophores/absorbers themselves. Rather, these pathology differentiating agents have the property of interacting with the tissue being imaged and altering its optical, *e.g.*, scattering/fluorescence/absorption properties. In this case, the scatterers/fluorophores/absorbers are ***intrinsic components of the tissue*** the optical properties of which have been altered as a result of the interaction with the pathology differentiating agent, rather than the added agents (as is the case in the methods of Klaveness *et al.*).

In view of the foregoing, it is evident that Klaveness *et al.* fail to teach or suggest each and every element of claims 1 and 6, and claims depending therefrom. Accordingly, Applicant respectfully requests that this section 102(b) rejection, be reconsidered and withdrawn.

Rejection of Claims 3, 11, and 13 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 3, 11 and 13 under 35 U.S.C. §103(a) as being unpatentable over Klaveness *et al.* in view of Deckert *et al.* In particular, the Examiner is of the opinion that "[t]o select a cervical tissue sample as the tissue sample as suggested by Deckert et al (see col. 8, lines 19-22) would have been obvious since Klaveness states that the tissue may be monitored *in vivo.*"

Applicant respectfully traverses the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following arguments is respectfully requested.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applicant respectfully submits that, as indicated above, Klaveness *et al.* fail to teach or suggest methods that employ a pathology differentiating agent ***which interacts with the tissue***

that is being imaged to alter its optical characteristics, as required by Applicant's pending claims. Moreover, Klaveness *et al.* teach away from the claimed invention by teaching that other methods of imaging tissue, *i.e.*, methods that employ particulate materials which are scatterers/fluorophores/absorbers themselves, have been successful. Thus, an ordinarily skilled artisan reading Klaveness *et al.* would not have been motivated to look for other methods of imaging tissue *in vivo*, nor would the ordinarily skilled artisan have a reasonable expectation of success in arriving at Applicant's invention.

Moreover, the secondary reference relied on by the Examiner, namely Deckert *et al.*, does not make up for the deficiencies in the primary reference. Specifically, Deckert *et al.* disclose an apparatus and means for the visual inspection of cervical tissue samples. Nowhere do Deckert *et al.* teach or suggest methods that employ a pathology differentiating agent ***which interacts with the tissue that is being imaged to alter its optical characteristics***, as required by Applicant's pending claims.

For the foregoing reasons, the combination of Klaveness *et al.* and Deckert *et al.* does not lead to the claimed invention since the cited references simply do not teach or suggest all of the claim limitations, and cannot lead to the claimed invention. Accordingly, rejection of the pending claims under 35 U.S.C. §103 is believed to be improper and Applicant respectfully requests that it be reconsidered and withdrawn.

Rejection of Claims 4 and 14 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 4 and 14 under 35 U.S.C. §103(a) as being unpatentable over Klaveness *et al.* in view of Modell *et al.* In particular, the Examiner is of the opinion that "[t]o select an esophagus tissue sample as the tissue sample as suggested by Modell *et al.* (see col. 26, lines 30-38) would have been obvious since Klaveness states that the tissue may be monitored

through use of an endoscope.

Applicant respectfully traverses the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following arguments is respectfully requested.

As indicated above, not only do Klaveness *et al.* fail to teach or suggest methods that employ a pathology differentiating agent ***which interacts with the tissue that is being imaged to alter its optical characteristics***, as required by Applicant's pending claims, but they also teach away from the claimed invention by teaching that other methods of imaging tissue, *i.e.*, methods that employ particulate materials which are scatterers/fluorophores/absorbers themselves, have been successful. Thus, an ordinarily skilled artisan reading Klaveness *et al.* would not have been motivated to look for other methods of imaging tissue *in vivo*, nor would the ordinarily skilled artisan have a reasonable expectation of success in arriving at Applicant's invention.

Moreover, the secondary reference relied on by the Examiner, namely Modell *et al.*, does not make up for the deficiencies in the primary reference. Specifically, Modell *et al.* disclose an apparatus and means for the visual inspection of esophagus tissue samples. Nowhere do Modell *et al.* teach or suggest methods that employ a pathology differentiating agent ***which interacts with the tissue that is being imaged to alter its optical characteristics***, as required by Applicant's pending claims.

For the foregoing reasons, the combination of Klaveness *et al.* and Modell *et al.* does not lead to the claimed invention since the cited references simply do not teach or suggest all of the claim limitations, and cannot lead to the claimed invention. Accordingly, rejection of the pending claims under 35 U.S.C. §103 is believed to be improper and Applicant respectfully requests that it be reconsidered and withdrawn.

Rejection of Claims 5, 8, and 15 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 5, 8, and 15 under 35 U.S.C. §103(a) as being unpatentable over Klaveness *et al.* in view of Kaplan. In particular, the Examiner is of the opinion that "[t]o select an ear tissue sample as the tissue sample as suggested by Kaplan (see col. 8, lines 7-10) would have been obvious since Klaveness states that the image may be acquired from light transmitted through a part of the body (e.g. an ear lobe)."

Applicant respectfully traverses the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following arguments is respectfully requested.

As indicated above, not only do Klaveness *et al.* fail to teach or suggest methods that employ a pathology differentiating agent ***which interacts with the tissue that is being imaged to alter its optical characteristics***, as required by Applicant's pending claims, but they also teach away from the claimed invention by teaching that other methods of imaging tissue, *i.e.*, methods that employ particulate materials which are scatterers/fluorophores/absorbers themselves, have been successful. Thus, an ordinarily skilled artisan reading Klaveness *et al.* would not have been motivated to look for other methods of imaging tissue *in vivo*, nor would the ordinarily skilled artisan have a reasonable expectation of success in arriving at Applicant's invention.

Moreover, the secondary reference relied on by the Examiner, namely Kaplan, does not make up for the deficiencies in the primary reference. Specifically, Kaplan discloses an apparatus and means for the visual inspection of ear tissue samples. Nowhere does Kaplan teach or suggest methods that employ a pathology differentiating agent ***which interacts with the tissue that is being imaged to alter its optical characteristics***, as required by Applicant's pending claims.

For the foregoing reasons, the combination of Klaveness *et al.* and Kaplan does not lead to the claimed invention since the cited references simply do not teach or suggest all of the claim

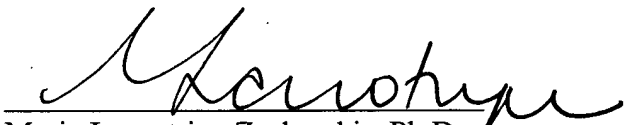
limitations, and cannot lead to the claimed invention. Accordingly, rejection of the pending claims under 35 U.S.C. §103 is believed to be improper and Applicant respectfully requests that it be reconsidered and withdrawn.

SUMMARY

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested.

If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



Maria Laccotripe Zacharakis, Ph.D.
Limited Recognition Under 37 C.F.R. §10.9(b)
Attorney for Applicant

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
(617) 227-7400
Dated: November 25, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Please replace the paragraph beginning at page 1, line 24 with the following re-written paragraph:

-- The conventional clinical process of optical examination have very limited capabilities in detecting cancerous and pre-cancerous tissue lesions. This is due to the fact that the structural and metabolic changes, which take place during the development of the ~~decease~~ disease, do not significantly and with specificity alter the color characteristics of the pathological tissue.

Please replace the paragraph beginning at page 15, line 31with the following re-written paragraph:

--For the clinical use of the methods of the invention, the different implementations of image capturing module described above can be integrated to conventional optical imaging diagnostic ~~devises~~ devices. Such ~~devises~~ devices are the various medical microscopes, colposcopes and endoscopes, which are routinely used for the *in vivo* diagnostic inspection of tissues. Imaging of internal tissues of the human body requires in most cases the illumination and imaging rays to travel along the same optical path, through the cavities of the body. Due to this fact, in the common optical diagnostic ~~devises~~ devices the tissue's surface reflection contributes substantially in the formed image. This limits the imaging information for the subsurface characteristics, which are in general of great diagnostic importance. This problem becomes more serious especially in epithelial tissues such as the cervix, larynx, oral cavity etc, which are covered by fluids such as mucus and saliva. Surface reflection also obstructs the detection and the measurement of the alterations in the tissue's optical properties, provoked after the administration of agents which enhance the optical contrast between normal and pathologic tissue. More specifically, when a special agent alters selectively the scattering characteristics of the pathologic tissue, the strong surface reflection that takes place in both pathologic (agent responsive) and normal (agent non responsive) tissue areas, occludes the diagnostic signal that originates from the interaction of the agent with the subsurface features of the tissue. In other

words, surface reflection constitutes optical noise in the diagnostic signal degrading substantially the perceived contrast between agent responsive and agent non responsive tissue areas.

Please replace the paragraph beginning at page 16, line 14 with the following re-written paragraph:

--Based on the above, the effective integration of the method to imaging diagnostic ~~devises~~ devices, requires embodiments of appropriate optics that ensure the elimination of the contribution of surface reflection to the captured image. Figure 4 illustrates a schematic diagram of a medical microscope consisted from a light source (LS), a magnification selection mechanism (MS), an eyepiece (EP) and a mount for attaching the image capturing module (CA), (detector(s), readout electronics etc). For the elimination of the surface reflection a pair of linear polarizers is employed. The incident to the tissue light (LS), is linearly polarized by passing though a linear polarizer (LPO). The surface reflected light (TS), has the same polarization plane with the incident to the tissue light (Fresnel reflection). By interposing the other linear polarizer to the optical path of the rays that are remitted from the tissue and form the optical image of the object, with its polarization plane perpendicular to the polarization level of the incident to the tissue light (IPO), the contribution of the surface reflection to the image of the object is eliminated. The light which is not surface-reflected enters the tissue, where due to multiple scattering, light polarization is randomized. Thus, a portion of the re-emitted light passes through the imaging polarization optics, carrying improved information for the subsurface features.--

Please replace the paragraph beginning at page 18, line 1 with the following re-written paragraph:

--The diagnostic examination of non-directly accessible tissues, located in cavities of the human body (ear, cervix, oral cavity, esophagus, colon, stomach), is performed with the aid of common clinical microscopes. In these ~~devises~~ devices the illumination-imaging rays are near co-axial. More specifically, the line perpendicular to the exit point of light into the air, and the line perpendicular to the objective lens, form an angle of a few degrees. Due to this fact, these microscopes operate at a specific distance from the subject (working distance), in which the illuminated tissue area, coincides with the field-of-view of the imaging system. These microscopes are found to be inappropriate in cases where tissue imaging through human body cavities of small diameter and at short working distances, is required. These technical limitations

are also constituting serious restricting factors for the successful clinical implementation of the method described herein. As it has been discussed above, elimination of surface reflection results in a substantial improvement of the diagnostic information, obtained from the quantitative assessment of marker-tissue interaction kinetics. If a common clinical microscope is employed as the optical imaging module, then due the above mentioned Illumination-imaging geometry, multiple reflections are occurring in the walls of the cavity, before the light reaches the tissue under analysis. In the case of colposcopy, multiple reflections are much more intense, since they are mainly taking place onto highly reflective blades of the speculum. Recall that the latter is inserted into the vagina to facilitate the inspection of cervix.--

In the claims:

Please amend claims 1 and 6 as follows:

1. **(Amended)** A method for monitoring the effects of a pathology differentiating agent on a tissue sample, comprising:

applying a pathology differentiating agent on a tissue sample, wherein said pathology differentiating agent interacts with said tissue sample and alters its optical characteristics; and

monitoring the rate of change of light reflection from said tissue sample over time, thereby monitoring the effects of a pathology differentiating agent on a tissue sample.

6. **(Amended)** A method for the *in vivo* diagnosis of a tissue abnormality in a subject, comprising

contacting a tissue in a subject with a pathology differentiating agent, wherein said pathology differentiating agent interacts with said tissue sample and alters its optical characteristics;

exposing said tissue in said subject to optical radiation; and

monitoring the intensity of light emitted from said tissue over time, thereby diagnosing a tissue abnormality in a subject.